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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/393,173	09/09/99	CURIEL	D D6163

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HM22/1213

EXAMINER

CONNELL, Y

ART UNIT	PAPER NUMBER
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1633

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DATE MAILED: 12/13/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/393,173	Applicant(s) Curiel et al.
	Examiner Yvette Connell Albert	Group Art Unit 1633

Responsive to communication(s) filed on _____.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1-10 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-10 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for making a vector encoding the bax gene and expressing the gene in tumor cells in vitro, does not reasonably provide enablement for administering a pharmacologically effective dose of this recombinant adenoviral vector therapy to treat any individual having a pathophysiological state. The specification does not enable any person skilled in the art or to which it most nearly pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 2 is drawn towards a pharmaceutical composition comprising a recombinant adenoviral vector encoding a pro-apoptotic bax gene in a pharmaceutically acceptable carrier, which implies that the product is used for gene therapy.

Claim 3 is drawn towards a method of treating an individual having a pathophysiological state, by administering a pharmacologically effective dose of recombinant adenoviral encoding pro-apoptotic bax gene.

Claims 4-8 are drawn towards a method of treating an individual having a neoplastic disease, specifically ovarian cancer, by administering this recombinant adenoviral vector therapy in a pharmacologically effective dose.

Claims 9-10 are drawn towards a method of sensitizing tumor cells to chemotherapy and radiotherapy in an individual by the administration of a pharmacologically effective dose of a pharmaceutical composition comprising a recombinant adenoviral vector encoding a pro-apoptotic bax gene in a pharmaceutically acceptable carrier. Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

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Nature of the invention. The claims are drawn to a method of treating an individual having a pathophysiological state, by administering to such an individual a pharmacologically effective dose of a recombinant adenoviral encoding a pro-apoptotic bax gene, in a pharmaceutically acceptable carrier. Since the claims recite administration of a pharmacologically effective dose to an individual, it is construed as a method for gene therapy.

State of the prior art. At the time of filing, there was no confirmed success in any human gene therapy trial, including trials using AV as the gene delivery vehicle. "In 1990, the first clinical trials for gene therapy approaches to combat disease were carried out. Although there are more than 200 clinical trials worldwide with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story". (Verma, Inder, M; Somia, Nikunji. Nature 389. 239-242 (1997)). W. French Anderson, Nature 392. 25-30 (1998) states: Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The field of gene therapy was and remains one of ongoing development. Thus, gene therapy is highly unpredictable.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. No disease was successfully treated using rAV vector gene therapy. This is reflected by several subsequently published reviews, at least one of which is mentioned.

W. French Anderson (Nature 392 S, 25-30, 1998) teaches that: "the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make".

Breadth of the claims. The claims are extremely broad, encompassing treatment of any and all individuals having a pathophysiological state. Applicant is proposing to treat several neoplastic diseases, notably ovarian

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cancer, by administering a pharmacologically effective dose of recombinant adenoviral vector encoding a pro-apoptotic bax gene.

Working examples. No working example is disclosed in the specification of the claimed invention which would enable the invention as claimed. While the specification provides excellent in vitro examples and impressive results based on these in vitro experiments, it fails to give sufficient evidence for the in vivo treatment encompassing administering a recombinant adenoviral vector encoding pro-apoptotic bax gene and the ensuing results. The one in vivo example given does not enable the invention since the nude mice were given ovarian cancer cells already pre-treated with the recombinant adenoviral vector encoding the bax gene, after which the mice were irradiated. It may have been more instructive to administer the ovarian cancer cells in vivo, wait until a tumor was established, then administer a therapeutically effective dose of the recombinant adenoviral vector encoding the bax gene and compare with irradiation before, during or after vector therapy. The in vivo example as listed pre-supposes that an individual would be subjected to ex-vivo gene therapy, and if this is the nature of the invention, then the specification as disclosed was misleading.

While the specification discloses a mammalian patient, preferably a human patient, the applicant must remember that: humans are not simply large mice. Studies in experimental animals may not necessarily predict the toxicology of vectors in humans. Crystal, R. G; Science 270, 404-410 (1995). As noted in a recent review by the NIH report on gene therapy: although animal investigations are often invaluable, it is not always possible to extrapolate directly from animal experiments to human studies.

Guidance in the specification. The specification fails to provide an enabling disclosure because it fails to provide adequate guidance that would have been accepted by the artisan in regard to the efficacious delivery of useful genes for treatment of any human disorder. It is incumbent upon applicants to provide sufficient and adequate teachings present within the specification for such therapeutic regimens. The specification fails to provide therapeutic routes of vector administration. While it is noted that in the mouse test system, ex-vivo vector therapy resulted in the alteration of an immune response, no indication is present that such a system has any clinical

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correlate. Thus the teachings and guidance present in the specification as a whole represent an initial investigation into the feasibility of the development of a useful means of executing gene therapy which awaits development to the practical level.

In the application, applicants have not taught that neoplastic diseases can be effectively treated by using the claimed vector. Given the highly unpredictable nature of both the *in vivo* regulation of gene expression in general and modulation of immune response in particular, in the absence of appropriate and specific guidance, the practitioner would have been required to have exercised a vast amount of experimentation in the practice of the full scope of what is claimed.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seth et al, in view of Kirshenbaum et al. Applicant claims a recombinant adenoviral vector encoding a pro-apoptotic bax gene, in a pharmacologically effective dose, in a pharmaceutically acceptable carrier.

Seth et al discloses an adenoviral vector which can be used and engineered to contain and express other genes that may be useful for eradicating tumor cells in which the vector is expressed via the toxic effects of the expressed genes. Some genes which can be used in the adenoviral vector include HSVTK, No-synthase, GADD 45, p15, mdm2, Rb, BAX, IL2, GMCF, p53-antisense, Her/Neu2 antisense, and Erb4 antisense(pg.21, ln 27-35).

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Seth et al teaches the recombinant adenovirus vector containing the gene of interest is administered in a pharmaceutically acceptable carrier.

At the time the claimed invention was made, Seth taught that a recombinant adenovirus vector could be used to introduce a gene into a subject afflicted with a tumor that has shown resistance to drugs, to inhibit proliferation of tumor cells, and that the amount of adenovirus vector effective to inhibit cell proliferation of actively proliferating cells would vary depending upon the cell types.

There would be a reasonable level of success in making and using an adenoviral vector with the bax gene as claimed, because Kirshenbaum et al demonstrated the ability to successfully introduce the bcl-2 gene, the anti-apoptotic gene which is another related family member of the bax gene family, into cardiac myocytes via recombinant adenoviral vector therapy.

At the time the invention was made it would have been *prima facie* obvious to one of ordinary skill in the art to make and use a recombinant adenovirus with the bax gene, since recombinant adenoviruses deliver with high efficiency and uniformity. Thus by introducing a pro-apoptotic bax gene in a recombinant adenoviral vector one would have expected high efficiency and uniformity of expression.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 7:30 to 4:00(Eastern time). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell


DEBORAH J. CLARK
PATENT EXAMINER